General

Guideline Title

Central nervous system opportunistic infections. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011.

Bibliographic Source(s)

Nelson M, Manji H, Wilkins E. Central nervous system opportunistic infections. In: British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. HIV Med. 2011 Sep;12(Suppl 2):8-24. [128 references]

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- January 4, 2016 – Noxafil (posaconazole) : The U.S. Food and Drug Administration (FDA) is cautioning that differences in dosing regimens between the two oral formulations of the antifungal Noxafil (posaconazole) have resulted in dosing errors. To help prevent additional medication errors, the drug labels were revised to indicate that the two oral formulations cannot be directly substituted for each other but require a change in dose. Direct mg for mg substitution of the two formulations can result in drug levels that are lower or higher than needed to effectively treat certain fungal infections.

Recommendations

Major Recommendations

Level of evidence (I–IV) ratings are defined at the end of the "Major Recommendations" field.

Cryptococcus neoformans

Diagnosis

- All individuals with a positive serum cryptococcal antigen should have a lumbar puncture performed (III).
- A positive cerebrospinal fluid (CSF) cryptococcal antigen is the most sensitive diagnostic test for cryptococcal meningitis (III).
- All patients undergoing a CSF examination for suspected cryptococcal meningitis should have manometry performed (III).
- Although fungal susceptibilities should be requested initially, the decision to switch therapy should not be based on the antifungal minimal inhibitory concentrations (MIC) alone but requires supportive laboratory or clinical markers of an impaired response to therapy (IV).

Treatment

Induction

- Standard induction therapy of cryptococcal meningitis is with amphotericin B, usually combined with flucytosine 100 mg/kg/day (Ib).
- Liposomal amphotericin B 4 mg/kg/day intravenously is the preferred amphotericin B preparation on the basis of lower nephrotoxicity than conventional preparations (III).
- Fluconazole plus flucytosine or the use of voriconazole or posaconazole may be considered where standard regimens fail or are not tolerated (IV).

Management of Raised Intracranial Pressure

- CSF manometry should be performed on all patients at baseline or if any signs of neurological deterioration occur, and serial lumbar punctures or neurosurgical procedures are indicated for individuals with an opening pressure >250 mmH_2O (III).

Maintenance

- The preferred maintenance regimen is fluconazole 400 mg once a day orally, started after approximately 2 weeks of induction therapy (Ib).
- The fluconazole dose is then reduced to 200 mg once a day after 10 weeks (III).
- A lumbar puncture at 2 weeks and extension of induction therapy until CSF cultures are negative can be considered in select individuals with poor prognosis at baseline or a poor initial clinical response to induction therapy (IV).

Prophylaxis

- Routine prophylaxis for cryptococcal disease is not recommended (IV).

Impact of Highly Active Antiretroviral Therapy (HAART)

- All individuals diagnosed with cryptococcal disease should receive HAART (IIb), which should be commenced at approximately 2 weeks, after commencement of cryptococcal treatment, when induction therapy has been completed.

Toxoplasma gondii

Diagnosis

- Radiological imaging aids diagnosis. Magnetic resonance imaging (MRI) is preferable to computed tomography (CT) (III).
- Single photon emission computed tomography (SPECT) may also be helpful in excluding the possibility of primary central nervous system lymphoma (PCNSL) (III).
- If there is not a contraindication to lumbar puncture a positive CSF polymerase chain reaction (PCR) for *T. gondii* helps establish a diagnosis but has only moderate sensitivity (III).

Treatment

- First line therapy for toxoplasma encephalitis is with pyrimethamine, sulphadiazine, folinic acid for 6 weeks followed by maintenance therapy (Ib).
- For patients allergic to or intolerant of sulphadiazine, clindamycin is the preferred alternative agent (Ib).
- Alternative therapies include trimethoprim-sulphamethoxazole alone (TMP-SMX, co-trimoxazole), atovaquone combined with sulphadiazine or pyrimethamine, but there is limited experience with these (III).
- Lack of response to 2 weeks of treatment, clinical deterioration or features that are not typical of toxoplasma encephalitis should lead to consideration of a brain biopsy (IV).

Prophylaxis

- Human immunodeficiency virus (HIV) patients with a CD4 count of <200 cells/μL and positive toxoplasma serology require prophylaxis against toxoplasma encephalitis (IIb).

Impact of HAART

- Primary and secondary prophylaxis can be discontinued when the CD4 count is repeatedly above 200 cells/μL (Ib).

Progressive Multifocal Leukoencephalopathy (PML)

Diagnosis

- MRI appearances and John Cunningham (JC) virus detection by polymerase chain reaction (PCR) in a CSF sample are sufficient to make a diagnosis in most cases and avoid the need for a brain biopsy (III).

Treatment

- HAART is the only intervention that has improved clinical outcomes with PML (III).

Cytomegalovirus (CMV)

Diagnosis

- MRI scanning and CSF PCR are the preferred diagnostic tests (III).

Treatment

- Ganciclovir with or without foscarnet is the treatment of choice (III).
- HAART should also be instituted after initial anti-CMV therapy (III).

Prophylaxis

- Prophylaxis against CMV encephalitis/polyradiculitis is not required but HAART is likely to decrease the incidence of these conditions (IV).

Definitions:

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well designed quasi-experimental study
III	Evidence obtained from well designed non-experimental descriptive studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Clinical Algorithm(s)

A clinical algorithm titled "Management of HIV Patients Presenting with Focal Neurology and CD4 Count <200 cells/μL" is provided in the original guideline document.

Scope

Disease/Condition(s)

- Central nervous system (CNS) opportunistic infections

    - *Cryptococcus neoformans* infection (cryptococcal meningitis)
    - *Toxoplasma gondii* infection (cerebral toxoplasmosis)
    - Progressive multifocal leukoencephalopathy (PML)
    - Cytomegalovirus (CMV) encephalitis and polyradiculitis
- Human immunodeficiency virus (HIV) seropositivity

Guideline Category

Diagnosis

Management

Prevention

Treatment

Clinical Specialty

Infectious Diseases

Internal Medicine

Neurology

Pathology

Preventive Medicine

Radiology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To help physicians in the United Kingdom investigate and manage human immunodeficiency virus (HIV)-seropositive patients suspected of or having a central nervous system (CNS) opportunistic infection

Target Population

Human immunodeficiency virus (HIV)-seropositive patients suspected of or having a central nervous system (CNS) opportunistic infection

Interventions and Practices Considered

Diagnosis

1. *Cryptococcus neoformans* infection
    - Serum cryptococcal antigen (latex agglutination method)
    - Lumbar puncture
    - Manometry

- Cerebrospinal fluid (CSF) fungal culture
- Fungal susceptibility testing (minimal inhibitory concentrations [MICs])

2. *Toxoplasma gondii* infection
    - Imaging (magnetic resonance imaging [MRI], computed tomography [CT], single photon emission CT [SPECT])
    - Lumbar puncture
    - Polymerase chain reaction (PCR) testing in CSF
    - Brain biopsy
3. Progressive multifocal leukoencephalopathy (PML)
    - MRI scanning
    - John Cunningham (JC) virus detection by PCR in a CSF sample
4. Cytomegalovirus (CMV) infection
    - MRI scanning
    - CSF PCR

Treatment/Prophylaxis/Management

1. *Cryptococcus neoformans* infection
    - Liposomal amphotericin B combined with flucytosine
    - Fluconazole plus flucytosine
    - Voriconazole
    - Posaconazole
    - Maintenance therapy
    - Highly active antiretroviral therapy (HAART)
2. *Toxoplasma gondii* infection
    - Pyrimethamine, sulphadiazine, and folinic acid
    - Clindamycin for sulphadiazine allergy or intolerance
    - Alternative therapies: trimethoprim-sulphamethoxazole (TMP-SMX), atovaquone combined with sulphadiazine or pyrimethamine
    - Prophylaxis using TMP-SMX and dapsone plus pyrimethamine
    - Discontinuing primary and secondary prophylaxis based on CD4 count
3. PML: HAART
4. CMV infection
    - Ganciclovir with or without foscarnet
    - Institution of HAART after initial anti-CMV therapy

Major Outcomes Considered

- Sensitivity and specificity of diagnostic tests
- Relapse rate
- Response rate
- Morbidity and mortality
- Resolution of infection
- Adverse events related to therapy

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The PubMed database was searched under the following heading: HIV or AIDS and central nervous system infection or space-occupying lesion

or meningitis or encephalitis or pneumonitis and/or *Cryptococcus neoformans*, cryptococcosis, *Toxoplasma gondii*, toxoplasmosis, progressive multifocal leukoencephalopathy, cytomegalovirus or CMV. The authors' own collections of reprints and meeting abstract books were also searched.

All information considered had to have been published in a peer review journal or presented at an international human immunodeficiency virus (HIV) meeting in abstract form. Inclusion/exclusion criteria essentially required that the information was relevant to the diagnosis, treatment or prevention of the specified opportunistic infection in HIV-positive individuals. Information of relevance to other related immunocompromised groups was also taken into consideration if the section authors felt relevant. Case reports were included and the review was not restricted only to clinical trials or meta-analyses. Search dates were from 1980 to January 2011.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
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III	Evidence obtained from well designed non-experimental descriptive studies
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Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of central nervous system (CNS) opportunistic infections in human immunodeficiency virus (HIV)-seropositive individuals

Potential Harms

- Flucytosine is associated with haematological toxicity and daily blood counts are required with monitoring of flucytosine levels.
- Standard amphotericin B is associated with renal toxicity, and where possible should be replaced by liposomal amphotericin B as the first choice agent.
- Physicians have to balance the risk of human immunodeficiency virus (HIV) progression against the hazards of starting highly active antiretroviral therapy (HAART), which include toxicities, side effects, immune reconstitution inflammatory syndrome (IRIS) and drug interactions.
- Corticosteroids should not be used routinely in toxoplasmosis as they cloud the diagnostic therapeutic trial.
- False positive cryptococcal antigen may occur in the presence of rheumatoid factor, heterophile antibodies, anti-idiotypic antibodies and *Trichosporon asahii* (*beigelii*) infection.
- Refer to Table 2.3 in the original guideline document for potential interactions between drugs used in treatment of central nervous system (CNS) opportunistic infections and antiretroviral drugs.
- Refer to Appendix 1 in the original guideline document for additional side effects of certain drug formulations.

Contraindications

Contraindications

- Refer to Appendix 1 in the original guideline document for contraindications of certain drug formulations.
- In patients presenting with mass lesions, lumbar puncture is often contraindicated due to raised intracranial pressure.

Qualifying Statements

Qualifying Statements

- These guidelines are primarily intended to guide practice in the United Kingdom and related health systems. Although it is hoped they can provide some guidance in developed countries there are some important distinctions in this environment and individual recommendations may not be as applicable in this setting.
- In the appendices in the original guideline document there is an A–Z of drugs used in the management of opportunistic infections. This is intended as a guideline but readers are advised to follow the discussion of dosing and the evidence for specific treatments provided in the text. In some cases alternative treatments are provided in the appendix in the original guideline document. These are not discussed in the text and these are mainly of historical interest and readers should be aware that these are not, in general, supported by the evidence base for treatments discussed in the text. It should also be noted that as evidence of drug toxicity, interactions, pregnancy risk and cost is rapidly evolving the table should be considered in association with the updated summary of product characteristics (SPC) for the agent and other relevant sources of drug information.
- Recommendations based upon expert opinion have the least evidence but perhaps provide an important reason for writing the guidelines: to produce a consensual opinion about current practice. It must, however, be appreciated that such opinion is not always correct and alternative practices may be equally valid. The recommendations contained in these guidelines should therefore be viewed as guidelines in the true spirit of the term. They are not designed to be restrictive nor should they challenge research into current practice. Similarly, although the British HIV Association (BHIVA) Opportunistic Infection Guidelines Group seeks to provide guidelines to optimize treatment, such care needs to be individualized and the authors have not constructed a document that they would wish to see used as a 'standard' for litigation.
- The clinical care of patients with known or suspected opportunistic infections (OIs) requires a multidisciplinary approach, drawing on the skills and experience of all healthcare professional groups. Moreover, these guidelines emphasize that inpatients with human immunodeficiency virus (HIV)-related disease often need rapid access to a variety of diagnostic tests and radiological interventions that may not be immediately available at local hospitals. Furthermore, expert interpretation of these tests by supporting specialties such as radiology, histopathology, microbiology and virology is often required. Optimal care of opportunistic infection can only be achieved by the close cooperation of these healthcare professionals and unless all are intimately involved in the care of patients, it is likely that the outcome will be less favourable. In keeping with BHIVA standards for HIV clinical care, patients needing inpatient care for HIV-related disease should ordinarily be admitted to an HIV centre or the relevant tertiary service in liaison with the HIV centre.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Mobile Device Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2011 Sep

Guideline Developer(s)

British HIV Association - Disease Specific Society

British Infection Association - Professional Association

Source(s) of Funding

British HIV Association

Guideline Committee

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Financial Disclosures/Conflicts of Interest

The British HIV Association (BHIVA) has a clear policy of declarations of interests within the Association:

- BHIVA requires that all members of guidelines writing groups, as well as any expert external peer reviewers, must declare all interests and membership of other committees retrospectively on an annual basis, to give protection to individuals working as members of writing groups.
- All members of guidelines writing groups must undertake a declaration of interests prior to serving on a writing group and this declaration is confirmed and repeated at the publication of each set of completed guidelines published.
- The details given in declaration forms are retained on a register at the Secretariat and can be made available for publication, if required.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British HIV Association (BHIVA) Web site . Also available as a smartphone app from the BHIVA Web site .

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on July 30, 2014. This summary was updated by ECRI Institute on January 6, 2016 following the U.S. Food and Drug Administration advisory on Noxafil (posaconazole).

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